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## Original Article

# Hypovitaminosis D in patients with Crohn's disease<sup>☆</sup>



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### ABSTRACT

**Objective:** Vitamin D has been widely studied as a mediator of the immune response, becoming evident the prevalence of hypovitaminosis D in patients with Crohn's disease. This work aims at evaluating the serum levels of vitamin D in patients suffering from Crohn's disease in a southeast region of Brazil.

**Methods:** It is a prospective study, with statistical analysis of the values of serum vitamin D measured between April 2014 and April 2015 in patients with Crohn's disease. Individuals with mild anal complaints, without any colorectal involvement, comprised the control group.

**Results:** One hundred and four patients whose average age was 40.6 years were evaluated, being 56 (53.8%) female and 48 (46.2%) male. The average serum vitamin D level was 21.6 ng/mL, with standard deviation 13.85. The control group was comprised by 66 individuals, whose average age was 48.9 years. With 38 (57.6%) female and 28 (42.4%) male. In this group the average serum vitamin D level was 40.9 ng/mL. Statistical significance was demonstrated with  $p < 0.0001$ .

**Conclusion:** There was high prevalence of hypovitaminosis D in patients with Chron's disease, when compared to the control group. Hypovitaminosis D was not evidenced in patients in the latter group.

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## Hipovitaminose D em pacientes portadores da doença de Crohn

### R E S U M O

#### Palavras-chave:

Doença de Crohn  
Doença inflamatória intestinal  
Vitamina D sérica  
25(OH)D

**Objetivo:** A vitamina D tem sido amplamente estudada como mediadora da resposta imune, tornando-se evidente a prevalência de hipovitaminose D em pacientes com doença de Crohn. Este trabalho objetiva avaliar os níveis séricos de vitamina D nos pacientes com portadores de doença de Crohn em uma região do sudeste do Brasil.

**Métodos:** Trata-se de estudo prospectivo, com análise estatística dos valores da vitamina D sérica dosados entre Abril de 2014 e Abril de 2015 em pacientes com doença de Crohn. Indivíduos com queixas anais leves, sem qualquer acometimento colorretal, compuseram o grupo controle.

**Resultados:** Foram avaliados 104 pacientes, cuja média de idade foi de 40,6 anos, sendo 56 (53,8%) mulheres e 48 (46,2%) homens. O nível sérico de vitamina D médio foi 21,6 ng/mL, com desvio-padrão de 13,85. O grupo controle foi composto por 66 indivíduos, cuja média de idade foi 48,9 anos, com 38 (57,6%) mulheres e 28 (42,4%) homens. Neste grupo o nível sérico médio de vitamina D foi 40,9 ng/mL. Foi demonstrada significância estatística com  $p < 0,0001$ .

**Conclusão:** Houve elevada prevalência de hipovitaminose D em pacientes com doença de Crohn, quando comparados ao grupo controle. Não foi evidenciada hipovitaminose D entre os pacientes deste último grupo.

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## Introduction

Crohn's disease is an intestinal inflammatory disease characterized by chronic intestinal inflammation of autoimmune character and uncertain etiology.<sup>1-7</sup> However, there is proven importance of the interaction between genetic and environmental factors in the triggering of the aberrant cellular immune response through Th1, Th17 cells and their pro inflammatory cytokines.<sup>1-3,7-11</sup>

In the context of cellular immunity, the discovery of the presence of vitamin D receptor (VDR) in the macrophages and lymphocytes, has opened a new path for research concerning autoimmune diseases.<sup>1-3,7-13</sup>

Vitamin D is a steroid hormone derived from cholesterol, obtained, mainly through solar exposition to beta-ultraviolet rays.<sup>1,7-12</sup> However, there is also a small acquisition from dietary intake.<sup>1,7-9,11</sup> This steroid is metabolized in the liver and subsequently in the epithelium of the renal proximal tube in its active form, the calcitriol (1,25OH<sub>2</sub>D). It has been evidenced that the serum vitamin D, in most part of it (85-90%) carried by the vitamin D carrier protein (DCP), has a significant role in the cellular immune response.<sup>1</sup> By diffusion, the vitamin D enters in the defense cells and is activated by 1 $\alpha$ -hydroxylase in 1.25(OH)<sub>2</sub>D<sub>3</sub> (Vitamin D<sub>3</sub>) and 1.25(OH)<sub>2</sub>D (Vitamin D<sub>2</sub>).<sup>1</sup> They form a complex when linked to the vitamin D receptor which activates the gene transcription, which act on the cellular immune response through the inhibition of T cells.<sup>1,3,9-11</sup> Suppressed, the Th1 and Th17 cells, determine the reduction of production and release of their pro-inflammatory cytokines, such as IFN $\delta$ , IL2, IL12 and IL17.<sup>1,3,9-12</sup>

Besides the inhibitory effect to these cells, the activated DCP complex, also stimulates the proliferation of T-regulatory

cells (T-reg), regaining then, the gastrointestinal immunological homeostasis.<sup>1,3,9-11</sup>

When evaluated the role of vitamin D in innate immunity, it has been found that the activation of the receptors of the membrane toll-like receptors (TLR) of macrophage by intestinal bacteria result in the conversion and bioavailability of active vitamin D, besides the increase of the expression of DCP and antimicrobial peptides, such as cathelicidins and defensins.<sup>1,3,9,11</sup>

The classification of serum vitamin D concentration ranges from severe deficiency to toxic levels, according to reference values, as demonstrated in Table 1.<sup>1,2,8</sup>

Several studies have demonstrated the prevalence of hypovitaminosis D in patients suffering from Crohn's disease.<sup>2,4-6,8,14-17</sup> In this context, data, still uncertain, show interference of serum vitamin D low levels in the appearance and progression of the disease.<sup>2,3,9-11,18,19</sup>

Aiming at carrying out data surveying, as the first step toward the investigation of the relationship between vitamin D and Crohn's disease in the scenario of southern tropical countries, being able to, in the future, cooperate for the

**Table 1 – Clinical interpretation of serum vitamin D levels.<sup>1-3</sup>**

Serum vitamin D levels (ng/mL)	Clinical interpretation
≤10	Severe hypovitaminosis
11-20	Vitamin D deficiency
21-29	Vitamin D insufficiency
30-36	Vitamin D adequate values
≥60	Above limit values
100-150	Toxic values

developing of new tools to evaluate disease activity and even the treatment optimization, this study has as aim to evaluate serum vitamin D levels in patients suffering from Crohn's disease followed by the Discipline of Coloproctology of Hospital de Base in São José do Rio Preto/SP (FAMERP), comparing them to a control group.

## Methods

It is about a transversal study, carried out in São José do Rio Preto, a city located in the southeast region of Brazil, latitude 20°49'11" South, 489 m above the sea level.

Patients suffering from Crohn's disease were identified, with clinical, endoscopic and histopathological diagnosis, followed by the Coloproctology discipline of Hospital de Base de São José do Rio Preto/SP, of the Medical School of São José do Rio Preto, and afterwards, made a database with the serum vitamin D values dosed between April 2014 and April 2015, their age and gender. Similar data, in the same period, were collected from individuals with mild anal complaints, with no colorectal involvement, also assisted by the same medical team, comprising thus, the control group.

Serum vitamin D dosage was carried out by laboratorial exams, requested during the patients' follow up in the outpatient clinic. All the exams were carried out by the Central Laboratory of Hospital de Base of São José do Rio Preto/SP through electrochemiluminescence, considering insufficient levels of vitamin D, values lower than 30 ng/mL, according to data from the US National Kidney Foundation.

The data were submitted to descriptive statistical analysis, with values of media, median and standard deviation, and comparative analysis through Mann–Whitney non-parametric test, being considered statistical significance for values of  $p > 0.05$ .

## Ethical considerations

The study was approved by the Research Ethics Committee of the Medical School of São José do Rio Preto (CAAE: 31070614.7.0000.5415), and informed written consent was obtained from each subject before entering the study.

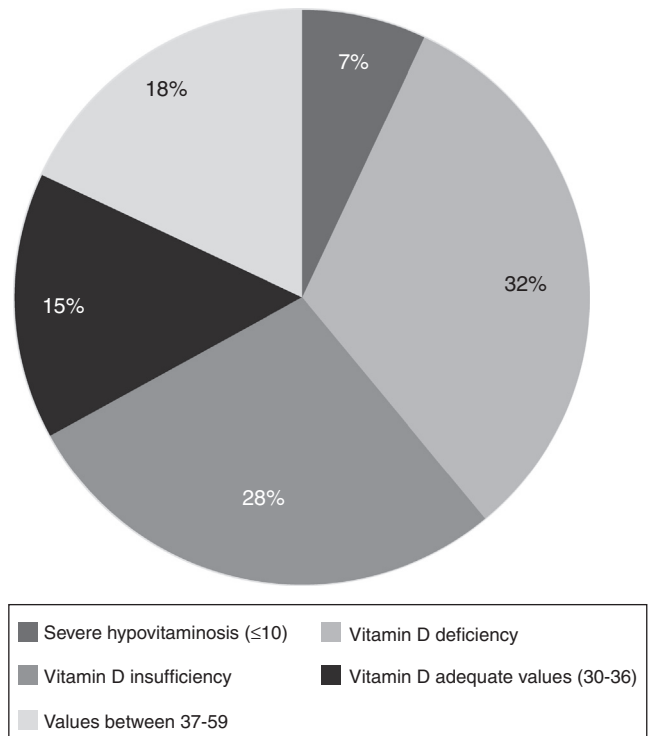
## Results

One hundred and four patients suffering from Crohn's disease were evaluated, whose average age was 40.6 years (SD 14.01), ranging from 15 to 75 years, being 56 (53.8%) female and 48 (46.2%) male. Among the individuals that comprised the control group, in a total of 66, the average age was 48.9 years (SD 13.97), ranging from 15 to 79 years, being 38 (57.6%) female and 28 (42.4%) male (Table 2).

The average serum vitamin D level among patients with CD, was 21.6 ng/mL, with SD of 13.85, ranging from 3.0 to 58.3 ng/mL. Fifty nine patients were identified with hypovitaminosis D, representing 66.3%. From these, seven (6.7%) presented serum vitamin D values lower or equal 10 ng/mL, thirty three (31.7%) between 11 and 20 ng/mL and twenty nine (27.9%) between 21 and 29 ng/mL. Only 16 (15.4%) presented

**Table 2 – Characteristics of groups concerning age and gender.**

Characteristics	Crohn's disease	Control
N	104	66
Age – Average (SD)	40.6 (14.01)	48.9 (13.97)
Gender		
Female (%)	56 (53.8%)	38 (57.6%)
Male (%)	48 (46.2%)	28 (42.4%)



**Fig. 1 – Serum vitamin D levels in patients with Crohn's disease.**

serum vitamin D value within adequate values, between 30 and 36 ng/mL (Fig. 1).

Among the control group's individuals, the serum vitamin D level was 40.9 ng/mL, with SD of 15.54. Serum vitamin D values considered adequate or above normality were presented by 52 patients (78.8%).

According to the comparative analysis between serum vitamin D values of both groups, through the Mann–Whitney test,  $p$  value was lower than 0.0001 (Table 3).

## Discussion

Epidemiologically, the literature data corroborate with the present study. The literature shows bimodal incidence of Crohn's disease in relation to age, affecting individuals from 15 to 40 years, and from 50 to 80 years.<sup>2,4,5,8,14,17,20</sup> There is also, agreement on the involvement between gender, with a higher percentage of women.<sup>2,8,14,17</sup> De Bruyn et al.<sup>8</sup> evaluated the vitamin D deficiency in 101 patients suffering from Crohn's disease, with average age of 41 years and mostly females. Similar epidemiological finding was demonstrated by

**Table 3 – Comparative analysis of serum vitamin D levels between groups.**

Serum vitamin D (ng/mL)	Crohn's disease (n = 104)	Control group (n = 66)
Average (SD)	21.626 (13.851)	40.950 (15.541)
Values		
Minimum	3.0	8.2
Maximum	58.3	105.0
Median	21.650	39.650
Confidence interval	18.929–24.323	37.127–44.773
Statistical significance (p)	<0.0001	

Ananthkrishnan et al.<sup>17</sup> and Azzopardi et al.<sup>20</sup> The characteristics between groups, patients with Crohn's disease and control group were similar.

The serum vitamin D level dosing of patients with Crohn's disease corroborated the findings of the great majority of studies already published, demonstrating the prevalence of hypovitaminosis D. The average serum vitamin D among the patients with Crohn's disease ranged, in the literature from 13.1 to 27 ng/mL<sup>2,4-6,8,14,17</sup> Yet, the control group presented serum vitamin D levels considered adequate.

The comparative analysis between the patients and the control group demonstrated high statistical significance, in agreement with data presented in the literature. Studies with such emphasis have been disclosed, mainly, from 2013, however up to now there have not been data concerning countries with a tropical climate in the southern hemisphere.

The hypovitaminosis D is common in high latitude regions.<sup>1,2,4,5,8,18,20</sup> Brazil is located in a low latitude area in the southern hemisphere, close to the tropics, showing favorable geographic position and high incidence of ultraviolet radiation. However, the present study obtained similar results to those found in countries located in high latitudes, demonstrating, thus, the presence of hypovitaminosis D in patients suffering from Crohn's disease, contrary to serum levels presented by the control group, being them, the very representatives of the country's geographic position. De Bruyn et al.<sup>8</sup> study, carried out in Holand, showed the presence of hypovitaminosis D among patients suffering from Crohn's disease, as well as Dumitrescu et al.<sup>4</sup> study, carried out in Romania.

The serum vitamin D dosing of this study, for both groups, took place during a whole year, involving all the seasons of the year, different levels of UV rays incidence and degrees of solar exposition, however, a better control of homogeneity in the collecting must be done in order to reduce possible biases. A study published by Raftery et al.<sup>19</sup> shows relationship between vitamin D and activity of Crohn's disease irrespectively of the season of the year. Therefore, hypovitaminosis D has presented itself prevalent in this group of patients, irrespectively of the region of the world or time of the year.

## Conclusion

In conclusion, the prevalence of low serum vitamin D levels has been evidenced among patients suffering from Crohn's

disease followed by the service of Coloproctology of Hospital de Base in São José do Rio Preto/SP, when compared to a control group, group which presented serum levels considered satisfactory.

The issue, however, still needs more comprehensive studies, mainly those who aim at evaluating serum vitamin D values related to clinical treatment and also the effects of vitamin D supplementation in the activity of the disease and healing of the mucous membrane. Thus, it will possible to evaluate in a relevant way, the vitamin D reposition in the Crohn's disease remission, optimizing these patients' treatment and corroborating for the improvement of their quality of life.

## Conflicts of interest

The authors declare no conflicts of interest.

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